THROMBO-ANGIITIS OBLITERANS: A STUDY OF THE VASCULAR LESIONS LEADING TO PRESENILE SPONTANEOUS GANGRENE.[1]

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There is an interesting group of cases characterized by typical symptoms which the Germans have described under the name "Spontan-gangrän." In 1879 von Winiwarter published the results of the pathological findings in one case, and reported an obliteration of practically all of the arteries of the leg by reason of a chronic proliferative process, due, in his opinion, to a new growth of tissue from the intima. He, therefore, proposed a new name for this condition, namely, "endarteritis obliterans." Patients afflicted with this so-called endarteritis obliterans present symptoms which are so characteristic that the diagnosis is not difficult. I have had occasion to observe some thirty cases of this disease, and have made pathological studies on the vessels obtained from eleven amputated limbs.

The disease occurs frequently, although not exclusively, among the Polish and Russian Jews, and it is in the dispensaries and hospitals of New York City that we find a good opportunity for studying it in its two phases, namely, in the period which precedes and in that which follows the onset of the gangrene. We usually find it occurring in young adults between the ages of twenty and thirty-five or forty years, and it is because the gangrenous process may begin at an early age that the names presenile and juvenile gangrene have been employed. In one class of cases there are rather characteristic attacks of ischemia. The patients complain of indefinite pains in the foot, in the calf of the leg, or in the toes, and particularly of a sense of numbness or coldness whenever the weather is unfavorable. Upon examination we see that one or both feet are markedly blanched, almost cadaveric in appearance, cold to the touch, and that neither the dorsalis pedis nor the posterior tibial artery pulsates. When the foot becomes warm some color gradually returns. Some patients complain of rheumatic pains in the leg, others are able to walk but a short distance before the advent of paroxysmal shooting, cramp-like pains in the calf of the leg makes it imperative for them to stop short in their walk. Some of these cases give the typical symptoms of intermittent claudication. After months—or, in some cases—even years have elapsed trophic disturbances make their appearance. It is at this stage that another rather unique symptom makes its appearance: one which gives the foot the appearance typical of erythromelalgia. In the pendent position a bright red blush of the toes in the anterior part of the foot comes on rather rapidly, extending in some cases to the ankle or slightly above. Soon a blister, hemorrhagic bleb, or ulcer develops near the tip of one of the toes, usually on the big toe, frequently under the nail, and when this condition ensues the local pain becomes intense. Such trophic disturbances may at times make little progress and last for months; sometimes, however, the skin in the neighborhood shows cyanotic discoloration, and dry gangrene of the whole toe is an early issue. Even before the gangrene, at the ulcerative stage, amputation may become imperative because of the intensity of the pain. The left leg is usually the first to become affected, although both limbs may show vascular disturbances almost simultaneously, and, when such is the case, the trophic changes, the ischemia or the reddening may give rise to a symptom-complex, often diagnosticated as Raynaud's disease. In short, after longer or shorter periods, characterized by pain, coldness of the feet, ischemia, intermittent claudication, and erythromelalgic symptoms, evidences of trophic disturbances appear which finally pass over into a condition of dry gangrene.

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[1] Read at a meeting of the Association of American Physicians, Washington, D. C., May 12 and 13, 1908.

HISTORICAL. Although the literature bearing upon the pathology of the disease just described is large, I wish to call attention only to some of the more important contributions. Von Winiwarter and Friedländer ascribed the closure of the vessels to a proliferation of the cellular and fibrous elements in the intima, and therefore proposed to call the lesion by the name "endarteritis obliterans." This theory has been accepted by most authors, and even to-day, it is to be found in all the text books. Somewhat later, Wilonski pronounced the opinion that the essential change in the vessel walls was due to a multiplication of the elastic fibers, and proposed the name "arteritis elastica" for the condition. Perhaps the most important contributions are those of Weiss and Zoege von Manteuffel, because these authors placed an entirely new interpretation upon the pathological findings. Basing his paper upon the studies of his assistant Weiss, von Manteuffel suggests that the extensive occlusion of the vessels in this disease is dependent upon a primary arteriosclerosis; that the obliterative process commences in the popliteal artery, where it owes its inception to the formation of a parietal white thrombus; and that by virtue of a gradual extension of the parietal thrombus downward, followed by organization, a picture resembling an obliterative endarteritis is produced. In his cases the veins did not seem to be involved in the process. Von Manteuffel comes to the conclusion that the thrombosis is due to desquamation of endothelial cells, and that this occurs where the intima shows most advanced lesions of arteriosclerosis, namely, somewhere in the popliteal artery. In spite of the veiws expressed by these latter authors, Sternberg, from the study of eight cases, is in accord with the old conception first suggested by von Winiwarter. Bunge, on the other hand, agrees with von Manteuffel, but his three cases appear to be instances of advanced arteriosclerotic change in elderly people rather than examples of the disease grouped under the name "endarteritis obliterans."

Two schools, then, have arisen among those who have made careful anatomical investigations: first, those who agree with von Winiwarter and who attribute the closure of the vessels to proliferation of the intima; and second, those who consider the process to be a peculiar type of arteriosclerosis in which desquamation of endothelium in the popliteal artery leads to the formation of parietal white thrombi and to occlusion of the arteries by direct peripheral extension from the primary focus.

During the last year and a half, through the kindness of Drs. Lilienthal, Gerster, and Sachs, of the Mt. Sinai Hospital, I have been able to make careful anatomical studies on eleven amputated lower extremities.[2] Although the results of the macroscopic and microscopic examination of the vessels agreed in part with the findings of other authors, a large number of additional facts were obtained which throw new light upon the pathology of the process. I may anticipate now by saying that from my own findings I can not agree with the veiws of von Winiwarter or von Manteuffel, but have come to the conclusion that we are dealing here with a thrombotic process in the arteries and veins followed by organization and canalization, and not with an obliterating endarteritis.

Gross Pathology. If we dissect out the vessels in these cases, we are struck by the fact that there is an extensive obliteration of the larger arteries and veins. Besides this, we find two other lesions which vary greatly in their intensity, namely, the periarteritis and the arteriosclerosis.

Upon making a large number of sections through such obliterated arteries and veins at different levels, we find certain characteristic appearances, which, in a general way, depend upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessel, and that appears to be pierced at one point (more rarely at a number of points) by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency, and does not at all resemble the crescentic or semilunar occluding masses typical of arteriosclerosis. The vessel itself is usually contracted, so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterative process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel, from the dorsalis hallucis almost into the popliteal.

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[2] Since reading this paper eight additional cases have been studied.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue. Frequently it becomes softer, more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives way to soft reddish masses which are evidently the results of recent thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others, it is of short extent and terminates in a long cone of recent thrombus.

It is interesting to note that the veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries, and this is particularly true of the collaterals of the posterior tibial, which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or the whole of the anterior tibial, of the dorsalis pedis, and dorsalis hallucis, an occlusion of the posterior tibial and plantar vessels, with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open, with the beginning of the occlusion in the upper part of this vessel or in the lower part of the anterior tibial. It is to be regretted that the termination of the process in the posterior vessels of the leg could not be determined in every instance because of the fact that amputation was done at a point where the posterior tibial was closed. In two cases, however, the popliteal and part of the posterior tibial vessels were found free; in others the popliteal could be felt to pulsate before the operation, and we can therefore conclude that in a number of cases at least the obturation does not attain the level of the popliteal artery.

Without giving a detailed description of the extent of the occlusion in all the cases, I may summarize by saying that we usually meet with obliteration of large territories with closure of the distal parts of the vessels, rather than the proximal; that there is often an involvement of some of the smaller branches, such as metatarsal and tarsal, but that the smallest arteries are free. The beginnings of the obliteration are not to be sought in the capillaries nor in the finest branches. If we follow the vessels upward, we frequently see a sudden cessation of the process, and in a number of instances we find that some 5 or 10 cm. of a vessel's length is closed and that the portions above and below are apparently normal.

It is from a study of the terminations of the obliterating masses of tissue, together with a study of those parts of the vessels which are apparently unaffected by the process, that most valuable information in regard to the pathology of the disease can be gained. As already indicated, there may be a sudden and abrupt change from occluded vessel to normal vessel; that is to say, the yellowish-brown tissue terminates in a rounded dome-like process which projects into an apparently normal lumen, or there may be a transition into red thrombotic masses or a conversion of the denser occluding tissue into tissue not unlike granulations. Such terminations occur at various points in the course of the arteries and veins. In one case the obliteration of the anterior tibial extended to about the middle of its course, and above this point its walls were almost normal save for some thickening of the intima. In another case the upper and lower terminations of the occluding tissue were found in the posterior tibial and in the peroneal arteries.

The peculiar appearances presented by these terminations, the apparently normal condition of the vessel above and below the occluding masses, and the transition into thrombosed areas, all speak in favor of the view that we are dealing with a thrombo-arteritis or thrombophlebitis, rather than with a proliferative or obliterating process derived from the intima of the arteries and veins. The microscopic studies gave sufficient exidence of the correctness of this conception.

Besides the lesion of occlusion there are two other striking changes, namely a certain amount of arteriosclerotic thickening and peri-arteritis. The arteriosclerosis is never pronounced except in those rare instances in which the patient has suffered from the disease for many years and has reached the latter part of the fourth decade. As a rule, we note but a very slight degree of whitening or thickening of the intima here and there in the patent portions of the vessels. In a very few cases small atheromatous patches are present. There were deposits of lime in but one case, and these were of small extent.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels, which I wish to discuss under the term "peri-arteritis." Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that liberation of the individual vessels by dissection is difficult. This adhesive condition is due to fibrous tissue growth, and varies considerably in its amount. At times we find little or no change about the occluded artery, at times fairly firm agglutination of the vessels in the sheath without much fibrosis, and at other times, so large an amount of connective tissue growth that isolation of the vessels or nerves becomes impossible, and the vascular structures make up one dense rigid cord. In a general way we may say that whenever both the collateral veins and the artery are occluded, we expect a fair amount of peri-arteritis, and that when but one vessel is affected, the perivascular change may be insignificant; and finally that the amount of peri-arteritis varies in the different cases as well as in the different territories affected by the disease.

HISTOLOGY. The pictures presented by the vessels that are involved in this process are so varied, that I must confine myself to the description of those rather typical changes that have suggested the true nature of the process to me, and from a study of which we can see the development of the lesion from its incipiency to its final maturation. I wish to point out: (1) The lesions of arteriosclerosis; (2) those that belong to the peri-arteritis; (3) the typical pictures found in the old obliterative process; (4) the differentiation of this lesion from the occlusive changes of arteriosclerosis; and (5) the various stages in the development of the occluding process from the beginning of the thrombosis to the final filling up of the vessel with dense fibrotic masses.

Both the arteries and the veins show varying degrees of thickening of the intima, the usual subendothelial changes with a fairly well marked hypertrophy of the internal elastic lamina without much proliferation of new elastic tissue in the thickenings of the intima. Of the two types of elastic tissue production pointed out by Jores, that which is dependent upon reduplication or hypertrophy of the internal elastic lamina is the more pronounced. Now and then in the older patients there are small plaques. Although the very small arteries may also be the site of thickening of the intima, this change is never sufficiently great to lead to complete or even marked obliteration of the lumen of the vessel. In the popliteal artery the formation of nodular thickenings is most extensive, but even here these are of moderate size.

The perivascular changes manifest themselves in a proliferation of connective tissue, in and around the adventitia, and are of two types, recent and old. Where the perivascular proliferation is active, the fixed connective tissue cells multiply and fibrous intercellular substance is deposited. Here and there small perivascular foci of lymphoid cells are found, but these do not seem to take an important part in the formation of connective tissue. In the old variety the fibrotic process appears to have come to a standstill, and the vessels and nerves are encased by dense bands of fibrous tissue, sometimes of a hyaline nature.

If we examine a cross-section of an artery or vein which is the seat of an old obliterative process, we often find an irregular, centrally placed lumen, a large amount of new-formed tissue occluding the original lumen, and certain changes in the media, the whole picture giving the impression that there is an extensive proliferation of the intima, namely an endarteritis obliterans (Fig. 1). From a consideration of the descriptions which are to follow, we will understand, however, that the new masses in the lumen are not derivatives of the intima, but owe their origin to organization of obliterating red thrombi. In the occluding tissue we find a fairly large number of capillaries, some blood pigment, and fibrous tissue which is either rich in cells (Fig. 2) or has already become sclerotic in nature. Where the process is oldest, there the capillaries are few, the connective tissue has become dense, the pigment has disappeared, and either in the middle or near the periphery of the obturating mass

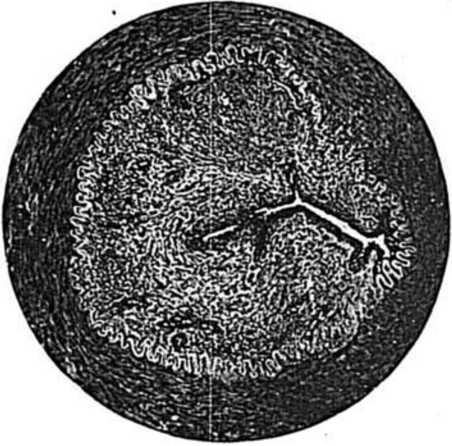


FIG. 1.—Obliterating tissue; old variety in dorsalis pedis; can be mistaken for "endarteritis obliterans;" old connective tissue; canalization; only slight vascularization of media. × 60.

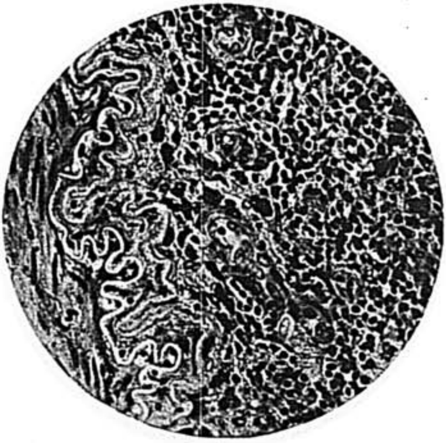


FIG. 2.—Obliterating tissue; young variety, in the posterior tibial artery; on the right the vascular young connective tissue with numerous cells and blood pigment; on the left the thickened intima and part of the media. × 250.

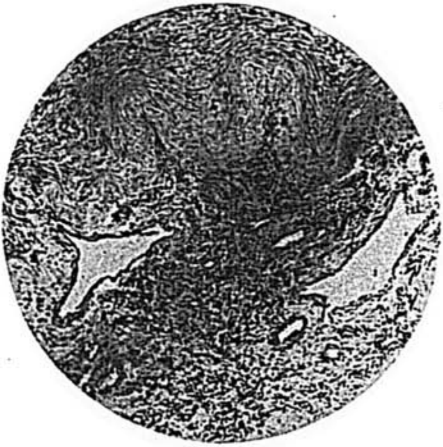


FIG. 3.—Old fenestrated obliterating tissue in the anterior tibial artery; above, the media and intima; below, blood spaces, dense connective tissue, and pigment. × 80.

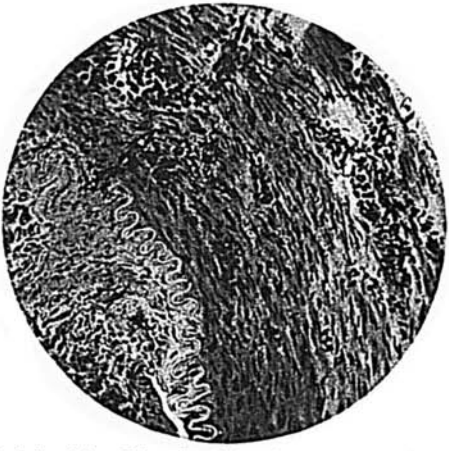


FIG. 4.—Lesions of the media in medium-sized arteries; many capillaries with or without slight perivascular lymphoid infiltration in the media; penetration of the internal elastic lamina by vessels which enter rather old typical occluding tissue. × 125.

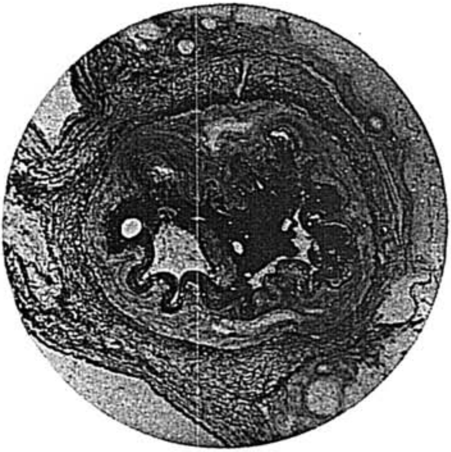


FIG. 5.—Obliterating arteriosclerotic process (orcein). The greater part of the lumen is occluded by tissue arising from the intima, and containing the typical elastic tissue found in arteriosclerosis; the small triangular clear area in the left part of the lumen contains a recent thrombus. × 40.

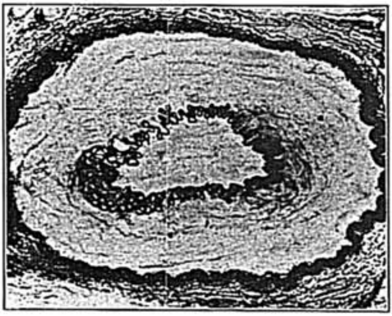


FIG. 6.—Absence of elastic tissue in thrombo-angiitis obliterans (orcein). The lumen is filled by old organized clot; no elastic-tissue production; below, elastic tissue in an arteriosclerotic plaque. × 40.

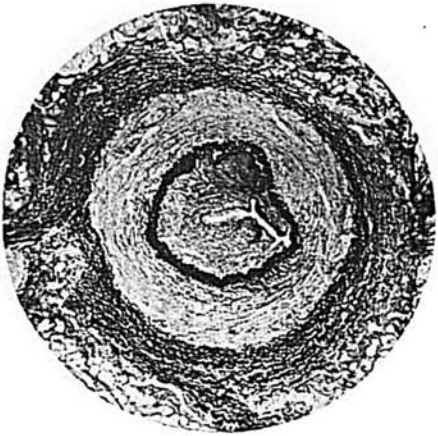


FIG. 7.—Elastic tissue in thrombo-angiitis obliterans. Perivascular disposition. × 40.

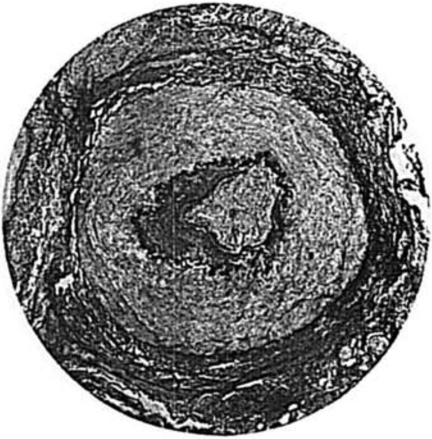
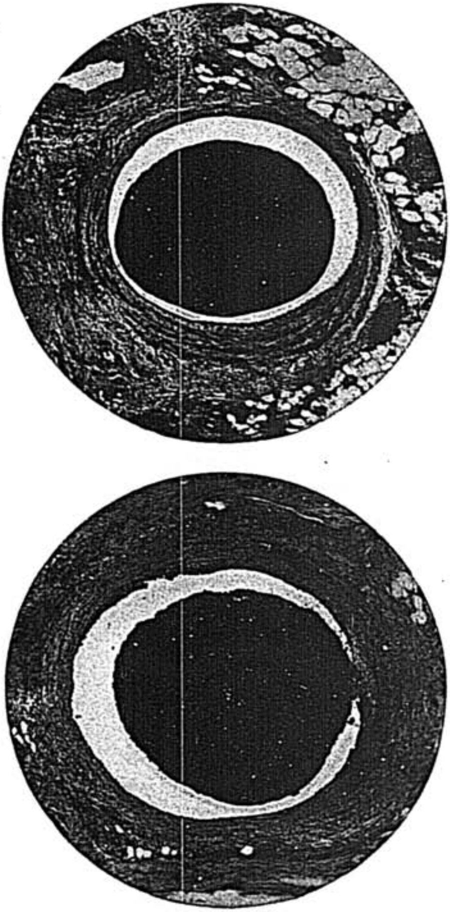


FIG. 8.—Thrombotic process at the site of an arteriosclerotic plaque in the posterior tibia artery; typical elastic tissue in plaque; absence of elastic fibers in the obliterating mass except around certain vessels. × 40.



Figs. 9 and 10.—Tied thrombus in anterior tibial vein. In Fig. 9 the termination of the clot (shrunken) lies in a portion of the vessel whose media is normal. In Fig. 10 the organizing process has commenced: the clot is adherent; with it there is the usual vascularization and slight cellular infiltration of the media. × 40.

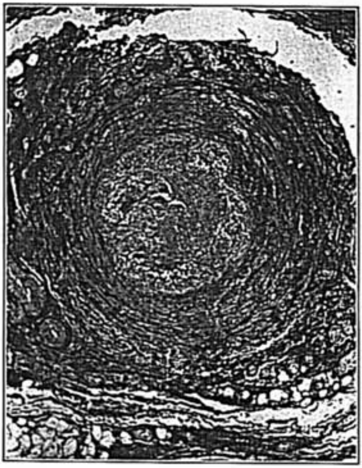


FIG. 11.—Early thrombosis with very slight changes in the media and intima; note the peripherally situated giant-cell foci. × 60.

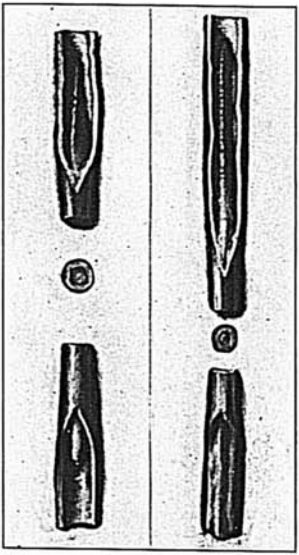


FIG. 12.—Termination of the occluding tissue of the peroneal and anterior tibial arteries in two different cases.

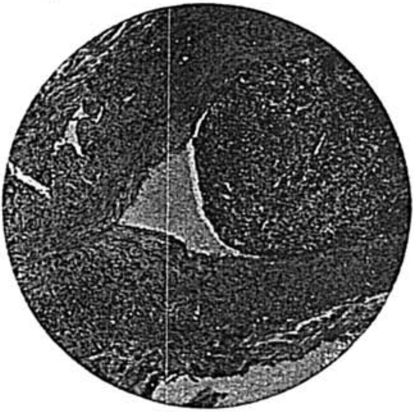


Fig. 13.—Central termination of an occluding mass in the peroneal artery, longitudinal section; vessel collapsed on the left, with the opposed intima layers in contact; the rounded extremity of an organized thrombus fills the distal half of the artery; slight thickening of the intima independent of the obliterating tissue. × 50.

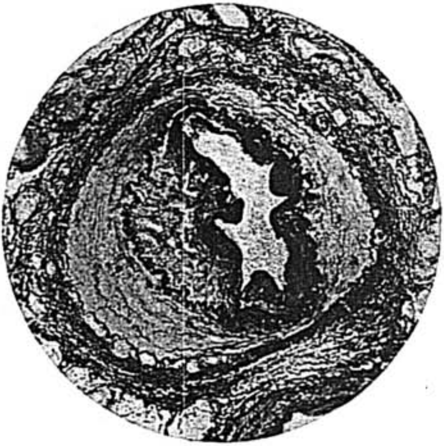


Fig. 14.—Old canalized thrombus giving an appearance similar to that found in obliterating arteriosclerosis; elastic-tissue formation around newly formed vascular channels. Obliterating tissue, which is very old and dense, would show a great many elastic fibers arranged parallel to the internal elastic lamina if the process were arteriosclerotic. The large channels are found to divide into smaller ones at other levels. × 40.

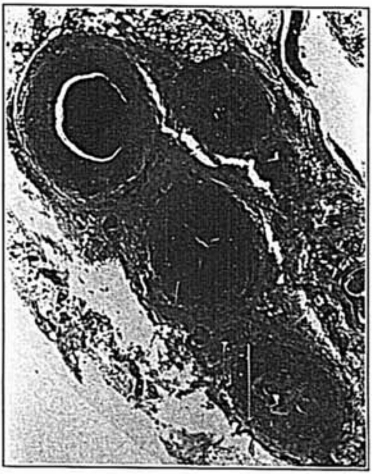


Fig. 15.—Artery and veins showing different stages of the obliterative thrombotic process; above there are two recently thrombosed veins; in the centre and below, an artery and vein are filled with sclerotic canalized tissue. × 18.

there is a large dilated vessel which is surrounded by connective tissue and which simulates the remnant of the original lumen. In other vessels there are large sinuses in the occluding mass (Fig. 3), or dilated vessels separated by dense connective tissue; or, there are atypical conformations in which two large blood spaces are separated by a septum that appears to spring from the intima of the vessel. The internal elastic lamina is thrown into marked folds, and between it and the connective tissue described, there may be a slight or moderate amount of fibrotic change in the intermediate layer of Eberth. The striking lesion of the media is the presence of capillaries with or without a small amount of lymphoid infiltration in their immediate vicinity (Fig. 4). Such capillaries may be present in small or in large numbers, depending upon the age of the process; where the occlusion is recent, the signs of activity in the media are striking, the capillaries plentiful, the cellular infiltration marked. The fine vessels come in from the adventitia, pass through the media, and penetrate the internal elastic lamina in order to vascularize the obturating mass.

What are the distinguishing features which enable us to differentiate an arteriosclerotic process from the lesions just described, and how can we establish the independence of the obturating masses from the intima from which most authors would have them arise? By the employment of the elastic tissue stains certain characteristics are brought to light which make it possible for us to say whether we are dealing with a thickening of the intima or with a new tissue lying in the lumen of the vessel. In arteriosclerosis we often find large obturating plaques which almost completely fill the vessel, the small space that is left being finally closed by a thrombus which becomes organized. It is not difficult to recognize such lesions as being arteriosclerotic when we note the large amount of elastic fibers in the plaque and note that these fibers are disposed for the most part parallel with the internal elastic lamina (Fig. 5). In the occluding masses of so-called endarteritis obliterans, we find either a total absence of elastic fibers, or, when such are present, a growth of fibers around the larger canalizing vessels, particularly about those which are thick-walled and old (Figs. 6 and 7).

The differences in the two lesions are well elucidated by the pictures which we obtain when we examine vessels that show a combination of marked arteriosclerosis and so-called endarteritis obliterans. At times we find occlusion of a vessel by obturating masses at the site of an arteriosclerotic plaque, and then the distinctions which I have pointed out become very apparent (Fig. 8). In such places the elastic fibers that belong to the thickened intima do not pass over into the occluding tissue except in those rare instances in which the penetrating vessel has ruptured such elastic fibers and has carried them for a short distance inward.

The most instructive histological pictures are those that are obtained in an examination of the vessels that are closed by transitional occluding tissue, and by this I mean obturation due to red thrombotic masses which can be traced into the softer brownish tissue and which finally may terminate in the dense old masses, the histology of which has already been discussed. In a number of cases and especially well marked in the vessels in an extremity which was amputated because of pain without gangrene, such transitions from areas of red thrombosis into the older stages were found. If we examine a vein or artery at or near the termination of the red thrombus, we find a fairly recent clot filling the lumen of the vessel without change in the vessel wall (Fig. 9). A short distance farther the clot becomes adherent in places and the corresponding portions of the media show beginning lymphoid infiltration and the earliest signs of vascularization (Fig. 10). At a point still farther removed, the aspect of the thrombosis has considerably changed. A number of miliary foci, not unlike miliary tubercles, make their appearance near the periphery, and there are evidences of organization such as the formation of capillary sprouts, fine capillaries, and fibroblasts (Fig. 11). The miliary foci present a central area of fibrin, and one or more giant cells (probably phagocytic in nature) with cells not unlike endothelial cells in a peripherial zone. Such giant-cell foci are but early stages in the process of organization. At another level the picture changes. The miliary foci gradually become lost, the vascularization of the clot becomes marked, the fibrin is almost absent, and numerous small round cells are scattered throughout. Here the media also shows quite a number of small capillaries with or without perivascular lymphoid infiltration. Whilst the fine vessels in the thrombus at this level are thin-walled, we soon note a change in their character. They become longitudinally disposed, here and there they connect with the media, they are surrounded by numerous round cells and fibroblasts and some blood pigment. These latter pictures correspond to the tissue which appears brownish and is not very firm. From this point on the transition into the old type is fairly rapid. The cells in the obturating mass disappear and the fibrous intercellular substance becomes abundant, some of the capillaries atrophy, others become dilated, forming large spaces with well defined walls; at times there are numerous sinuses giving a fenestrated appearance; at times there is a centrally placed vessel resembling a much diminished lumen of the original vessel, and sometimes such canalizing vessels are centrally placed. With this final maturation of the organizing process there are certain concomitant regressive changes in the media, namely, a diminution in the number of capillaries and the disappearance of alien cellular elements.

A detailed discussion of all the bizarre appearances that were found would take me too far, and I have therefore described only those changes which seem to me to be valuable in elucidating the nature of the occlusion, and which show that this is to be sought not in an endarteritis, but in the organization of obliterating thrombi. I have given in brief the stages in the development of the process, and have shown how the old typical pictures can be directly traced into the areas of old and recent thrombosis; further how the changes in the media are dependent upon vascularization of the clot and are not primary. What other evidences have we that establish the correctness of our view of the process? A histological study of some of the terminations of the obturating tissue, particularly of the abrupt variety, gives valuable information on this point. Thus if we make longitudinal sections through those rounded ends of occluding tissues which mark the cessation of the process in some of the vessels, we see how the closed portion of the vessel surrounds a vascular mass of young connective tissue and pigment; we note how the end of this mass rounds off, that it seems to be wholly independent of the intima except for points of junction by means of penetrating capillaries, and we are struck by the absence of pathological lesions just beyond the point of closure (Figs. 12 and 13).

We must not fail to interpret the nature of those pictures which would at first sight be mistaken for obliteration due to proliferation of the intima; namely, those in which there is a large canalizing vessel more or less centrally placed, surrounded by a fair amount of elastic fibers (Fig. 14). The paucity of elastic fibers in what would appear to be thickened intima, and the fact that the apparent remnant of the original lumen of the vessel usually divides at other levels into a number of smaller blood spaces, many of which finally communicate with the media, make it evident that we have here simply another product of the organizing thrombotic process.

Before closing the description of the vascular lesions it may be well to allude to some of the very interesting observations that were made in cases in which the thrombotic process was evidently of long duration. Here we frequently find that various stages in the organizing and thrombotic process may be represented not only in different vessels of the limb, but also in the separate members of a vascular sheath. Thus, the posterior tibial artery may be occluded by dense fibrotic canalized tissue through the greater part of its course, one of its accompanying veins showing an intermediate stage, another a very early process (Fig. 15). Still more striking are the appearances that were seen in the posterior tibial vessels of one case. Here the canalizing vessels had become very large and thick walled, and had become affected by the same thrombotic changes that had previously occurred in the parent vessel.

Pictures such as these just depicted not only point out the true nature of the process but are also suggestive of the historical development of the lesion. They tend to show that there are frequent relapses or recurrences of the thrombosis, now in this, now in that vessel, at one time extending upward in a vessel already diseased, at another time affecting even the canalizing vessels themselves.

The Nerve Lesions. The study of the nerves in these cases is of considerable importance, both because the symptom of pain is such a constant and distressing one, and because some of the clinical features, such as the red blush of the foot in the pendent position, the transitory ischemia, and the cramp-like sensations in the calf, have all been in turn referred to some spinal or peripheral nerve disturbance.

In general we may say that the nerve lesions are secondary, apparently dependent upon the fibrotic perivascular changes. Thus we find considerable connective tissue proliferation around the nerve bundles, thickening of the perineurium, and even atrophy of nerve fibers wherever the peri-arteritis is marked and where the nerves are intimately connected with the vessels. In such places degeneration of many nerve fibers can be demonstrated by the Marchi method. The oldest perivascular connective tissue proliferation is then usually accompanied by the most intense fibrosis of the nerve sheaths. The popliteal nerve is usually free, as also the internal popliteal; whereas the anterior tibial and posterior tibial are more frequently affected. The cases vary considerably in regard to the amount of nerve lesions. In some, in which the periarteritis is minimal, no change in the nerves could be demonstrated; in others some of the nerves were found embedded in a dense mass of connective tissue. As regards the extent of the process, this corresponds fairly well with the vascular territory which is involved.

GENERAL CONSIDERATIONS. Before entering upon a discussion of the genesis of the process, and before giving our views as to the possible etiology, it may be well to recall some of the more important facts that have been developed by the study of the pathological lesions. These may be summarized as follows: Most of the larger arteries and veins of the amputated limbs were found obliterated over a large extent of their course. The obliterative process can be studied at any stage in its development if enough vessels are examined. All stages in the occlusive change may occur in the various vessels of an extremity or at times in the same vessel in different parts of its course. The occlusion of the vessels is effected by red obturating thrombi; these become organized, vascularized, and canalized. The recent red thrombosis may involve large portions of arteries or veins and is not secondary to the gangrenous process. It occurs even when no gangrene is present.

Certain changes in the perivascular tissues, in the adventitia, media, and intima, regularly accompany the occluding process.

There is moderate thickening of the intima; this is never sufficient to cause marked narrowing of the lumina of the vessels, and does not seem to play any considerable role in the genesis of thrombotic process.

The media and adventitia show cellular infiltration and vascularization wherever thrombosis has occurred. The intensity of the cellular and vascular change seems in general to depend upon the activity of the organization of the clot; however, in some cases it seems to be sufficiently marked to make it appear that the same agent which calls forth the coagulation of the blood is also effective in producing the mesarterial lesion. The occluding masses frequently terminate abruptly in apparently normal vessels. The changes in the media never extend into the walls of the patent portions of the vessels; usually they terminate before the end of the obturating tissue or thrombus is reached; indeed, the dependence of the medial changes upon the organization of the thrombi can be demonstrated in many places.

As a result of the dilatation of a central canalizing vessel, and the fibrous change in the occluding tissue, a picture resembling that due to intense proliferation of the intima may be produced. By means of elastic tissue stains and a thorough study of the vessels at many levels it is comparatively easy to show that the obliterative process has its origin in a thrombus and differs in a number of essentials from the occlusive change due to arteriosclerosis.

From what has been said, we must needs regard the views of von Winiwarter and those who have agreed with him as fallacious, and have but to deal with the theory propounded by von Manteuffel. We would at first hand be led to the belief that the changes in the intima are in great part responsible for the thrombosis; for this is doubtless the case in the secondary closure by clot in cases of senile and diabetic gangrene. Zoege von Manteuffel takes the view that parietal white thrombi first lodge in the popliteal and gradually extend downward; that they remain mural in nature, are of the white variety, and are but rarely mixed with small red clots of recent origin. Practically every one of my cases furnished me with many evidences of the incorrectness of this conception. Thus, the large territories filled with red thrombi with their transitions into the old occluding masses, the frequent absence of any change in the upper parts of the anterior and posterior tibial arteries when very distal parts were occluded, and further, the presence of pulsation in the popliteal artery in some of the cases in which that vessel could not be examined, all speak against his assumption. We gain the impression that the obturation ascends rather than descends; for the firmest and oldest tissue is most frequently found in the distal parts and not infrequently terminates in young thrombi or soft rounded abrupt terminations in the middle or lower part of the leg. Finally, the presence of the same lesion in the veins, which Zoege von Manteuffel had evidently not encountered, could certainly not be explained in the light of his theory.

What then causes the extensive thrombosis of the veins and arteries? We are not able at this juncture to give a decisive answer on this perplexing point. Even to this day the determining causes of thrombosis are not completely understood, and it is therefore not surprising that here also we meet with difficulty. A number of factors must be taken into account, the arteriosclerotic change, the lesions of the media, the periarteritis, as pathological changes conducive to thrombosis; the external influences, as well as possible toxic conditions of the blood. We have already alluded to the fact that the changes in the intima do not appear to be responsible for the thrombosis. According to Lubarsch in his very recent summary of the literature on thrombosis, we must regard the changes in the intima as playing but a subsidiary role in this process; for, up to the present time it has not been clearly demonstrated that the endothelium contains any substance that can inhibit coagulation, nor has it been proved conclusively by animal experimentation that lesion of the intima alone suffices for the production of clot. Then again it is common occurrence to find extensive ulcerations and even calcareous plaques without the formation of thrombi. Even more significant is the fact that in arteriosclerosis the most extensive changes in the walls do not correspond to the site of thrombus formation.

In the vessels under consideration this independence of arteriosclerotic thickening and obliterating thrombosis is well illustrated, for in no place were we able to refer the origin of a clot to the presence of a thickened or diseased intima. Indeed, the popliteal artery which is apt to show the most marked arteriosclerotic change, is frequently free and patent. It becomes occluded only when the process has extended upward from its branches. Further, we frequently find complete occlusion of the vessels whose walls are practically normal; and above and below such points the intima of the patent vessel may show a fair amount of arteriosclerosis. The white parietal thrombi which von Manteuffel claims to have seen adherent to arteriosclerotic patches, were never met with in the very great number of sections which we studied. On the other hand, it would appear that some of the thickening of the intima could be attributed to the process of organization of the thrombi, and we believe it to be, in a measure, secondary to that process.

It is not my purpose to enter deeply into a discussion of all the factors that may be responsible for the thrombosis, for my studies on this particular phase of the subject are still incomplete. It is of considerable importance to determine what role syphilis may play in the production of the lesions. A history of this disease was not obtainable in a single case, and thus far I have been unable to demonstrate *Spirocheta pallida* in any of the sections.[3] However the periarteritis is rather suggestive, and requires further investigation. In a number of the cases cultures were made particularly from those portions of the vessels which showed the most active changes, and also from the hard sclerotic occluded portions, with negative results in every instance. It would seem therefore that at least the pathogenic bacteria are not present.

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[3] The final results of this investigation will be reported at a later date.

If we take a broad view of the pathological lesions, we see that we are dealing in main with the results of a healed process, namely, with vessels obliterated by dense connective tissue which has become canalized. In such vessels the thrombotic changes have disappeared, the cellular infiltration and vascularization of the media have diminished in intensity, leaving but a few capillaries behind; and the adventitia and peri-arterial tissues are either slightly thickened or converted into dense connective tissue. Besides this, however, there is the active process, that in which the thrombosis is recent. This is apparently of two varieties. In one of these the vessels are filled with blood clot over a large portion of their extent and there is active organization accompanied by that very slight cellular infiltration and capillary invasion of the media which make for the vascularization of the clot. The changes in the media terminate before the end of the clot is reached, so that some of the thrombus lies in apparently healthy vessel. Here we gain the impression that all the lesions are dependent upon the thrombus formation, and are present for the purposes of organization. In the second variety, however, the same thrombosis is accompanied by more intense infiltration of the media and more active peri-arteritis. In such places it would appear that the same determining cause which leads to the thrombosis also evokes the changes in the media, adventitia, and perivascular connective tissue.

We must not forget the influence of static factors. Indeed the slowing of the circulation alone is a very important agent in the production of thrombosis, and it is rather significant that we so often encounter this disease in the lower extremities and that in all but one of our cases the disease began on the left side where venous stasis is more marked. Doubtless, then, a number of agents are at work in the production of the occlusion. Whatever may be the cause of the thrombosis, we feel inclined to take the view that, although the mechanical conditions that obtain in the lower extremities and the arteriosclerotic changes may be factors, some additional agent, be it toxic or otherwise, is at the same time responsible for the production of the peri-arteritis and thrombosis.

Viewing the process from the standpoint of the pathological lesions, and considering certain facts obtained by clinical observation, it would seem most plausible to assume that certain territories of either the arteries or the veins become rather suddenly thrombosed, in a fashion similar to the thrombotic process that occurs in the superficial veins of the lower extremities. Thus, at one time the dorsalis hallucis and dorsalis pedis, or perhaps plantar arteries or veins, could become closed by red clot; and then the process of organization would take place. Perhaps after an interval of weeks or months a similar process would cause extension upward, or affect other arteries and veins, until, after a lapse of many months, or a year or more, practically all the larger vessels would become occluded. It is from a study of the age of the process in the various territories that we are led to this supposition. Here too as in the superficial thromboses there is more tendency for the larger vessels to be involved than for the very fine ones; and although the process seems to ascend, it probably does not originate in the capillaries or smallest arterioles, but begins in branches of moderate size. The attendent peri-arteritis could be regarded as being either secondary, or possibly, as being produced by the same causes that lead to the thrombosis. Certain it is that the peri-arteritis is intimately linked with the presence of occluding masses.

Taking the true nature of the lesion into consideration, I would suggest that the names "*endarteritis obliterans*" and "*arteriosclerotic gangrene*" be discarded in this connection, and that we adopt the terms "*obliterating thrombo-angiitis*" *of the lower extremities* when we wish to speak of the disease under discussion.

I wish to express my indebtedness to Dr. F. S. Mandlebaum, director of the pathological department of the Mt. Sinai Hospital, for the preparation of the photomicrographs which I have shown to elucidate certain points in my paper; I wish to thank Drs. Lilienthal, Gerster, and Sachs for giving me the opportunity of studying their cases, and to acknowledge with pleasure the valuable assistance rendered me by Miss Adèle Oppenheimer and Dr. Mark Cohn, volunteer assistants in the pathological laboratory of the Mt. Sinai Hospital.

ADDENDUM. Since writing this paper I have examined the vessels of eight additional cases of this disease, and have found still further corroboration of what has been said. In one of the extremities a little more than one-third of the anterior tibial was occluded by fairly red recent thrombotic masses; the uppermost portion of the vessel was patent, the distal end as well as the dorsalis pedis and hallucis being occluded by old canalized connective tissue. In another case, the occlusion was old in all of the distal parts of the arteries, recent in the upper part of the posterior tibial and popliteal arteries. The thrombotic process terminated abruptly at about the middle of the popliteal, and could also be traced into the origin of the anterior tibial, where its rounded organized end was found lying 1 cm. below the foramen in the interosseous membrane. The upper end of the occluding tissue that had ascended from the dorsalis hallucis was situated two inches above the ankle-joint, the intervening portion of the anterior tibial artery being patent.